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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,221	08/22/2001	Florence Marciacq	025219-342	1827

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EXAMINER

LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 12/09/2002

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/914,221

Applicant(s)

MARCIACQ ET AL.

Examiner

Patrick T. Lewis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-33 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3-4. 6) ☐ Other: ____

Detailed Action

Information Disclosure Statement

1. References cited on PTL-1449 with improper citations (i.e. no dates, source of publications, etc.) were not considered.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 16-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use or an intended, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compounds of formula (I) wherein

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R³ is derived from fluorescein, does not reasonably provide enablement of compounds of formula (I) wherein R³ is generically described as a label (other than labels derived from fluorescein), protein, enzyme, fatty acid, or peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Claims 1-11 are drawn to a process for manufacturing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment. The nucleotide derivative is further defined by the variable R² which is further defined by the

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variable R^3 wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid, or a peptide. Claims 12-15 are drawn to a morpholino-nucleotide of formula (I). Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide of formula (I). Claim 17 is drawn to the use of a morpholino-nucleotide of formula (I).

The nature of the invention requires a close look at that which is provided in the claims and the scope of the content encompassed by the claim language. The instantly claimed invention relates to a process for manufacturing a 3'-labelled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment.

Morpholino oligonucleotide analogs and their preparation are well known in the art. Production may be carried out on automated synthesizers. The oligonucleotide analogs may also incorporate probes. Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). Although the art teaches enzymes broadly, the innumerable possibilities incorporated by such a broad term as "enzyme" requires further guidance from the specification as to the nature of the enzymes.

A person of ordinary skill in the art would be an organic chemist or biochemist having a PhD.

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided

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to enable the use and making of a 3'-labelled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment wherein R^3 is generically described as a label (other than labels derived from fluorescein), protein, enzyme, fatty acid, or peptide. The diverse nature of labels, proteins, enzymes, fatty acids, and peptides requires further guidance from the instant specification as to which moieties included in the vast group are incorporated into the instantly disclosed nucleic acid fragment.

The working examples in the instant specification are limited to the synthesis of 3'-labelled nucleic acid fragments of formula (I) wherein R^2 is $-\text{CH}_2\text{-COOH}$, $-(\text{CH}_2)_4\text{-NH}_2$, or $-(\text{CH}_2)_4\text{NHR}^3$ in which R^3 is a group derived from fluorescein; use of morpholino T glycine for the analysis of DNA sequence; testing morpholino A putrescine and morpholino A fluorescein in sequencing; use of morpholino A putrescine (MATPP) and morpholino A fluorescein (MATPPF) for the template-dependent 3' labeling of DNA fragments, test of enzymatic incorporation of these compounds by three polymerases and a reverse transcriptase. This guidance is not seen to be sufficient to teach the skilled artisan in this field how to make and use compounds of formula (I) wherein R^3 is generically described as a label (other than labels are derived from fluorescein), protein, enzyme, fatty acid, or peptide.

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation and use of use compounds of formula (I) wherein R^3 is generically described as a label (other than labels are derived from

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fluorescein), protein, enzyme, fatty acid, or peptide. The lack of guidance provided by the instant specification as to the nature R^3 would indeed necessitate undue experimentation.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-17, 19, 21, 23, 25, 27, 29-31, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1 and 3 incorporate the parenthetical phrase "(DNA or RNA)". It is unclear if the terms included within the parentheses are intended to incorporate limitations into the claim. All claims and depending claims incorporating said parenthetical phrase are indefinite in all occurrences. The parenthesis should be removed.

Claims 1, 3, 10, 12-17, and 30-31 incorporate the phrases "derived from", "fluorescein derivatives", "biotin derivatives", "rhodamine derivatives", and/or "group derived from fluorescein". Applicant has failed to particularly point out the identity of the compounds and the modifications to said compounds which distinctly set forth the structural core modifications or chemical moieties effectuating said derivatization. In the absence of distinct modifications or derivatizing moieties, the terms "derived" and "derivatives" are indefinite in all occurrences since the metes and bounds of said "derivatives" and "derived" components cannot be ascertained.

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Claim 3 is drawn to a “process for sequencing a nucleic acid”. It is unclear whether this process is drawn to synthesizing a nucleic acid of a known sequence or drawn to a process for determining sequence of a nucleic acid which is unknown. The lack of clarity renders claim 3 and all subsequent depending claims indefinite.

In claims 4-5, 19, 21, and subsequent depending claims, it is unclear which “enzyme” is being referenced since claim 3, from which claims 4-5, 19, and 21 depend, recites “enzymatic polymerization” and “R³ is a group derived from ...a enzyme”.

Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide; however, no active steps are set forth to practice said process. In the absence of any positive active procedural steps, the skilled artisan would not be apprised of the metes and bounds of the said process.

Claim 17 provides for the use of a morpholino-nucleotide of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims which depend from an indefinite claim are indefinite and are rejected for the reasons set forth herein above under 35 U.S.C. 122, second paragraph.

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Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent

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6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claims 1-11 are drawn to a process for manufacturing a 3'-labeled nucleic acid fragment comprising the enzymatic incorporation of a nucleotide derivative having as a precursor a compound of formula (I), at the 3' OH end of the nucleic acid fragment. The nucleotide derivative is further defined by the variable R^2 which is further defined by the variable R^3 wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid, or a peptide. Claim 3 is drawn to a "process for sequencing a nucleic acid". It is unclear whether this process is drawn to synthesizing a nucleic acid of a known sequence or drawn to a process for determining sequence of a nucleic acid which is unknown. The examiner is interpreting the invention as being drawn to a process for synthesizing a nucleic acid of a known sequence. Claims 12-15 are drawn to a morpholino-nucleotide of formula (I). Claim 16 is drawn to a process for manufacturing a morpholino-nucleotide of formula (I).

Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

Torrence differs from the instantly claimed invention in that the morpholino-nucleotide of formula (I) is described generically and Torrence does not teach a method of preparation. These deficiencies are, however, addressed by Iversen and Meyer.

Iversen teaches antisense agents comprising nucleotide subunits joined by internucleotide backbone linkages which present the nucleotide bases for hybridization with target RNA sequences (column 5, lines 16-20). Iversen teaches various oligonucleotide analogs modified at the backbone, the sugar moiety, or the bases themselves. Such analogs include, for example, morpholino oligonucleotides (column 5, lines 36-45). The preparation of the antisense agents is well known in the art, and may often be conveniently carried out on automated synthesizers. Iversen further teaches a general procedure for synthesis of S-OD, C-5-P, and uncharged morpholino antisense oligonucleotides (column 5, lines 48-52; Example 1). A summary of a typical synthesis is as follows: 1 μ mol silica gel support column with the 3' base of the morpholino nucleotide analog linked by the 3'hydroxy group is inserted, and synthesis is carried out in a base by base fashion from the 3' to 5' direction (column 14, lines 17-22).

Meyer teaches oligonucleotides which have at least one cross-linking agent covalently attached to the oligonucleotide. The cross-linking function typically includes a linker arm and an electrophilic reactive group which, after complexing with the target sequence of DNA or mRNA is capable of reacting with the target DNA to form a covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization

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probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. The Klenow fragment and other enzymes known in the art are recognized as interchangeable. One would have been motivated to combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

12. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent 6,365,577 B1 (priority from Provisional application 60/105,695 filed October 26, 1998) (Iversen), and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer).

Claim 17 is drawn to the use of a morpholino-nucleotide of formula (I).

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Torrence teaches a morpholino-nucleotide of formula (I) used for fine-tuning in antitumoral chemotherapy wherein m is 0-4, Y is H, n is 1-15, Z is H or a C₁₋₅₀ hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms (column 3, lines 1-36; column 4, lines 31-68; column 5).

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covalent bond therewith (column 5, lines 16-25). The cross-linking agents may be attached to either the heterocyclic bases, to the sugars or modified sugars, or to the phosphate or modified phosphate moieties (column 5, lines 31-34). The preparation of modified sugars and of their respective "nucleosides" wherein such sugars or analogs are attached to a heterocyclic base (nucleic acid base) per se is known (column 6, lines 2-8). Meyer further teaches the utilization of the oligonucleotides as hybridization probes and evidence of sequence specific cross-linking to single stranded DNA (column 12, lines 7-18). Probes may be labeled by several methods typically used in the art. Typical probes include radioisotopes, fluorophores, chemiluminescent agents, and enzymes. The choice label dictates the manner in which the label is incorporated into enzymes. The choice label dictates the manner in which the label is incorporated into the probe (US 5,849,482; column 12, lines 19-44). The radioactive nucleotides can be incorporated into probes, for example, by using DNA synthesizers, by nick-translation, by tailing of radioactive bases in the 3' end of probes with terminal transferase, or by copying M13 plasmids having specific inserts with the Klenow fragment of DNA polymerase in the presence of radioactive dNTP's (column 12, lines 33-44).

It would have been obvious to one of ordinary skill in the art at the time of the invention combine the teachings of Torrence, Iversen, and Meyer to obtain the instantly claimed invention. The incorporation of a morpholino into a polymeric structure via 3' end is known in the art. The art teaches manufacture, modification via elongation, and sequencing using an automated synthesizer. One would have been motivated to

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combine the teachings to produce pharmaceuticals useful for treating proliferative cell disorders.

Conclusion

13. Claims 1-33 are pending. Claims 1-33 are rejected. No claims are allowed.

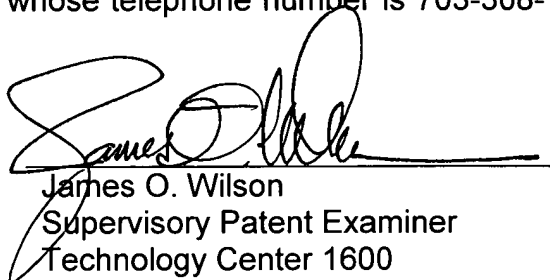
Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 10:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
December 3, 2002